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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 209/44, A61K 31/40, C07D 233/54

A1

(11) International Publication Number: WO 97/05110

(43) International Publication Date: 13 February 1997 (13.02.97)

(21) International Application Number: PCT/IB96/00783

(22) International Filing Date: 25 July 1996 (25.07.96)

(30) Priority Data:
95/09410 2 August 1995 (02.08.95) FR

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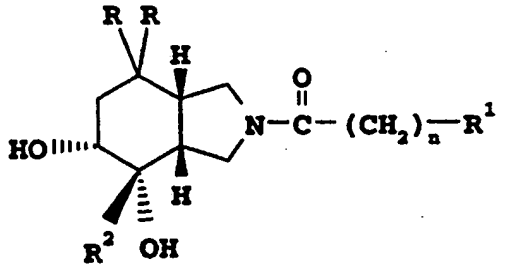
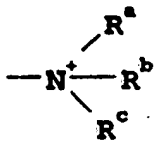
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PERHYDROISOINDOLE DERIVATIVES AS SUBSTANCE P AND NEUROKININE A ANTAGONISTS



(I)



(II)

, X^-

(57) Abstract

Compounds are described having formula (I) and salts and solvates thereof wherein R represents phenyl optionally substituted in the ring 2 or 3 position with fluorine, chlorine or methyl, R^1 represents a group $-NR^aR^b$ or an ammonio radical of structure (II), R^2 represents phenyl optionally substituted by one or more of halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy, and n represents an integer from 2 to 4. The novel compounds according to the invention simultaneously antagonize the effects of tachykinins on NK1 and NK2 receptors and are particularly advantageous therapeutic agents for the treatment of a variety of diseases and disorders, including those of the respiratory system.

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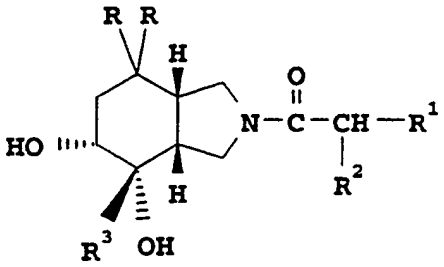
PERHYDROISOINDOLE DERIVATIVES AS SUBSTANCE P AND NEUROKININE A ANTAGONISTS

The present invention relates to novel perhydroisoindole derivatives which antagonize the effects of substance P and neurokinin A and are accordingly particularly advantageous in the therapeutic fields in which the NK1 and NK2 receptors are involved.

International patent application publication WO 94/22822 describes perhydroisoindole derivatives of general formula:

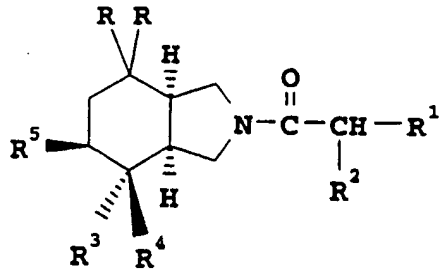


in which the symbols R are optionally substituted phenyl radicals, the symbols R^1 and R^2 represent various substitutions and the symbol R^3 represents a phenyl radical optionally substituted in 2-position. Such compounds are reported therein to antagonize the effects of neurokinin A.

Neurokinin A is involved in many pathologies, such as the transmission of pain, arthritis, asthma, inflammatory phenomena, psychoses, tension disorders, bladder disorders, cystitis, etc. The effects of neurokinin A are mainly mediated by the NK2 receptors.

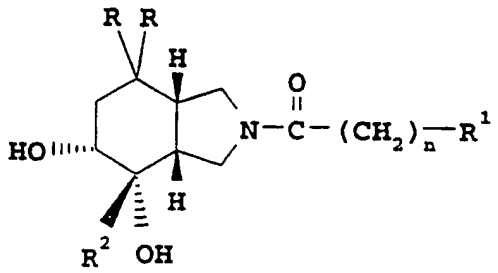
International patent application publication WO 93/21155 describes perhydroisoindole derivatives of

general formula:



in which the symbols R are optionally substituted phenyl radicals and the symbols R^1 and R^2 represent various substitutions, the symbol R^3 represents phenyl optionally substituted in the 2-position, the symbol R^4 is a fluorine atom or a hydroxyl radical and the symbol R^5 is hydrogen or hydroxyl or forms a bond with R^4. Such compounds are reported therein to antagonize the effects of substance P.

It has now been found that a small group of novel perhydroisoindole derivatives simultaneously antagonize the effects of tachykinins on NK1 and NK2 receptors. Thus, according to one aspect of the present invention, there is provided compounds of the general formula (I)

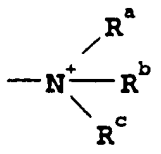


(I)

and salts and solvates thereof wherein

- the moieties R are identical and represent phenyl radicals optionally substituted in the ring 2 or 3 position with a fluorine or chlorine atom or a methyl group;

- R^1 represents a group $-NR^aR^b$ or an ammonio radical of structure:



, X^- (II)

in which X^- is an anion and R^a, R^b and R^c are the same or different and each independently represents a C_{1-4}alkyl or arylC_{1-4}alkyl group, or R^a and R^b, together with the nitrogen atom to which they are attached, form a saturated 4- to 6-membered heterocycle optionally containing a heteroatom selected from O, S, NH or NR^d (where R^d is C_{1-4}alkyl or arylC_{1-4}alkyl) in place of one of the ring CH_2 groups; or when R^1 represents a group $-NR^aR^b$ then R^a and R^b, together with the nitrogen atom to which they are attached, may also form an unsaturated 4- to 6-membered heterocycle optionally containing a heteroatom selected from O, S or N in place of one of the ring carbon atoms, or R^a and R^b, together with the nitrogen atom to which they are attached, may form a salt of an unsaturated 4- to 6-membered heterocycle wherein one of the ring carbon atoms is replaced with a group NR^d where R^d is as defined previously;

- R^2 represents a phenyl radical optionally substituted by one or more of halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy moieties; and
- n represents an integer from 2 to 4.

It is to be understood that herein the term "alkyl" as a group or part of a group means a straight or branched alkyl chain.

The term "aryl" as part of an arylC_{1-4}alkyl group may

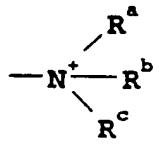
represent, for example, phenyl or phenyl substituted by one or more of halogen, C_{1-4}alkyl or C_{1-4}alkyloxy moieties.

Unless otherwise stated, the term "halogen" herein means chlorine, bromine, fluorine or iodine.

When R^1 represents a heterocyclic system suitable ring moieties include, for example, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholino, thiomorpholino or imidazolyl.

Preferred compounds of formula (I) include compounds in which R represents phenyl.

R^1 preferably represents an ammonio radical of structure:



, X^- (II)

where R^a, R^b, R^c and X^- are as defined hereinabove. Particularly preferred are such compounds in which R^c represents phenylC_{1-4}alkyl (e.g. benzyl) and R^a and R^b each independently represents C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated 4- to 6-membered heterocycle. Such compounds in which R^c represents benzyl and R^a and R^b each independently represents C_{1-4}alkyl (e.g. methyl) are especially preferred.

R^2 preferably represents a mono or disubstituted phenyl moiety, particularly where the substituent(s) is/are selected from halogen atoms (e.g. fluorine) and C_{1-4}alkyloxy (e.g. methoxy) groups. R^2 especially

represents a phenyl moiety substituted in the ring 2-position [particularly when substituted in the ring 2-position by a C_{1-4}alkyloxy (e.g. methoxy) group] and is preferably further substituted, more preferably when further substituted in the ring 5-position (for example by a C_{1-4}alkyloxy group such as methoxy or a halogen atom such as fluorine).

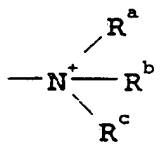
R^2 most preferably represents 2,5-dimethoxyphenyl or 5-fluoro-2-methoxyphenyl.

n is preferably 2 or 3, and is more preferably 3.

In the general formula (II), the anion represented by X^- may advantageously be a halide (chosen from chloride, bromide, fluoride or iodide) or alkylsulphonate anion or a benzenesulphonate anion optionally substituted in the benzene ring with one or more halogen atoms or alkyl or nitro groups.

A particular group of compounds of the invention are compound of the general formula (I) as depicted hereinabove wherein

- the moities R are identical and represent phenyl radicals optionally substituted in the ring 2 or 3 position with a fluorine or chlorine atom or a methyl group;
- R^1 represents an ammonio radical of the structure:



, X^- (II)

in which X^- is an anion and R^a, R^b and R^c are the same or different and each independently represents a C_{1-4}alkyl group or together with the nitrogen atom to

which they are attached form a saturated or unsaturated 4- to 6-membered heterocycle which may contain another heteroatom which is chosen from nitrogen, oxygen or sulphur and is optionally N-alkylated or N-benzylated when the second heteroatom is a nitrogen atom, or R^a, R^b and/or R^c represents a benzyl radical;

- R^2 represents a phenyl radical optionally mono- or disubstituted with a halogen atom or a C_{1-2}alkyl or C_{1-2}alkyloxy radical; and
- n represents an integer from 2 to 4.

Particular compounds of the invention are selected from the following:

(3aR,4R,5R,7aR)-2-(4-benzyldimethylammoniobutyryl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol bromide;
(3aR,4R,5R,7aR)-2-[4-(1-methyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol iodide;
(3aR,4R,5R,7aR)-2-[4-(1-benzyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol bromide;
(3aR,4R,5R,7aR)-2-[4-(3-benzyl-1-imidazolio)butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindol-4,5-diol bromide;
(3aR,4R,5R,7aR)-2-(3-benzyldiethylammoniopropionyl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol bromide; and
(3aR,4R,5R,7aR)-2-(4-benzyldimethylammonio-2-butyryl) 7,7-diphenyl-4-(5-fluoro-2-methoxyphenyl)perhydroiso-indole-4,5-diol bromide; and solvates thereof.

Other particular compounds of the invention are selected from the following:

(3aR,4R,5R,7aR)-4-(2,5-dimethoxyphenyl)-2-(4-dimethyl-

aminobutyryl)-7,7-diphenylperhydroisoindole-4,5-diol;
(3aR,4R,5R,7aR)-4-(2,5-dimethoxyphenyl)-2-[4-(1-pyrrolidinyl)butyryl]-7,7-diphenylperhydroisoindole-4,5-diol;
(3aR,4R,5R,7aR)-4-(2,5-dimethoxyphenyl)-2-[4-(1-imidazolyl)butyryl]-7,7-diphenylperhydroisoindole-4,5-diol;
(3aR,4R,5R,7aR)-2-(3-diethylaminopropionyl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol;
(3aR,4R,5R,7aR)-4-(5-fluoro-2-methoxyphenyl)-2-(4-dimethylaminobutyryl)-7,7-diphenylperhydroisoindole-4,5-diol;
(3aR,4R,5R,7aR)-4-(2,5-dimethoxyphenyl)-2-[4-(N-methylbenzylamino)butyryl]-7,7-diphenyl perhydroisoindole-4,5-diol; and
(3aR,4R,5R,7aR)-4-(5-fluoro-2-methoxyphenyl)-2-[N-methylbenzylamino)butyryl]-7,7-diphenylperhydroisoindole-4,5-diol; and salts and solvates thereof.

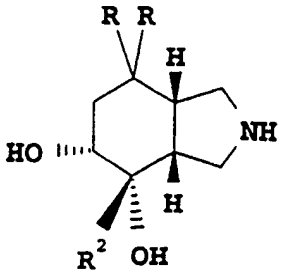
A preferred compound of the present invention is a salt of (3aR,4R,5R,7aR)-2-(4-benzyldimethylammoniobutyryl)-7,7-diphenyl-4-(5-fluoro-2-methoxyphenyl)-perhydroisoindole-4,5-diol, especially (3aR,4R,5R,7aR)-2-(4-benzyldimethylammoniobutyryl)-7,7-diphenyl-4-(5-fluoro-2-methoxyphenyl)perhydroisoindole-4,5-diol bromide

The compounds of general formula (I) may be obtained by the reaction of an acid of formula (III)

$$R^1-(CH_2)_n-COOH \qquad (III)$$

or a reactive derivative of this acid (in which n is defined as above and R^1 is a group NR^aR^b) with an

isoindole derivative of formula (IV)



(IV)

(in which the symbols R and R^2 are defined as above) or a salt thereof (eg the hydrochloride salt) followed, where required, by quaternization of the product thus obtained.

When the condensation is carried out with a reactive derivative of the acid of formula (III), the process is advantageously performed using the acid chloride, the anhydride, a mixed anhydride or a reactive ester in which the ester residue is a succinimido, optionally substituted 1-benzotriazolyl, 4-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl or phthalimido radical.

The condensation reaction is generally carried out at a temperature in the range of -40°C to +40°C, in an organic solvent such as a chlorinated hydrocarbon (e.g. dichloromethane, dichloroethane or chloroform), a hydrocarbon (e.g. toluene), an ether (e.g. tetrahydrofuran or dioxane), an ester (e.g. ethyl acetate), an amide (e.g. dimethylacetamide or dimethylformamide) or a ketone (e.g. acetone) or in a mixture of these solvents, in the presence of an acid acceptor, for example a nitrogen-containing organic base such as pyridine, dimethylaminopyridine, N-methylmorpholine or a trialkylamine (in particular diisopropylethylamine or triethylamine) or an epoxide (e.g. propylene oxide). It is also possible to perform the reaction in the presence of a condensing agent

such as a carbodiimide [for example dicyclohexyl-carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide], N,N'-carbonyldiimidazole or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or alternatively in an aqueous-organic medium in the presence of an alkaline condensing agent such as sodium bicarbonate.

The quaternization may conveniently be carried out by reaction with a compound of formula (V)

$$R^C\text{-}X \qquad (V)$$

in which R^C is as previously defined and X is a halogen atom or an alkylsulphonyloxy or phenylsulphonyloxy radical in which the phenyl moiety is optionally substituted with one or more of halogen, alkyl or nitro.

The quaternization reaction may generally be performed in an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether or dioxane), a nitrile (e.g. acetonitrile), an aromatic hydrocarbon (e.g. toluene), a ketone (e.g. acetone), an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol or ethanol) at a temperature in the range of about 20°C to the reflux temperature of the reaction mixture.

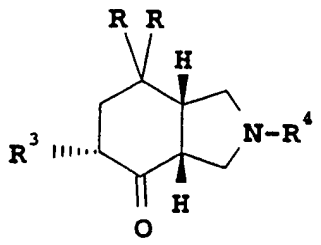
The acids of general formula (III) are either known or may be prepared according to the methods described below in the Examples.

The compounds of formula (IV) may be obtained by reacting an organometallic compound of formula (VI)

$$R^2\text{-}M \qquad (VI)$$

in which R^2 is defined as above, and M represents

lithium, or a radical MgX or CeX_2 in which X is a halogen atom with a compound of formula (VII)



(VII)

in which R is defined as above, R^3 is an optionally protected hydroxyl radical and R^4 is a protecting group, followed by the removal of all protecting groups.

The protecting group within R^3 may be any hydroxyl-protecting group whose installation and removal do not adversely affect the rest of the molecule. The protection may conveniently be carried out, for example, by an acetyl, trialkylsilyl or benzyl radical, or by a carbonate radical -COOR' in which R' is an alkyl or benzyl group.

R^4 may be any suitable amino-protecting group whose installation and removal do not adversely affect the rest of the molecule. Examples of suitable amino-protecting groups include alkyloxycarbonyl, optionally substituted benzyloxycarbonyl and benzyl groups, formyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, vinyloxycarbonyl, phenoxycarbonyl, 1-chloro-ethoxycarbonyl or chlorocarbonyl groups.

The reaction may conveniently be carried out in anhydrous medium, under the usual conditions for the reaction of organometallic compounds with a ketone, which do not adversely affect the rest of the molecule. The reaction may in particular be effected in an ether solvent, for example tetrahydrofuran or

ethyl ether, optionally in the presence of anhydrous cerium chloride, at a temperature in the range of about -78°C to 30°C. It will be understood that, depending on the nature of the protective group for the radical R^3, this protecting group may conveniently be removed simultaneously with the reaction between (VI) and (VII).

The subsequent removal of the protective radical R^4 may be carried out according to the usual methods. In particular, the installation and removal of the protective radicals may be carried out according to the methods described by T.W. Greene, Protective Groups in Organic Synthesis, A. Wiley - Interscience Publication (1991), or by McOmie, Protective Groups in Organic Chemistry, Plenum Press (1973).

The compounds of formula (VII) in which R^3 is a protected hydroxyl radical may be prepared as described in WO 94/22822 by analogy with the method described in EP 429,366 or in the Examples hereinafter.

It will be understood that the compounds of formulae (I), (IV) and (VII) may have several stereoisomeric forms. In order to obtain a product of general formula (I) in the form (3aR, 7aR), the isomeric forms are preferably separated at the level of the derivative of general formula (IV) or at the level of another intermediate bearing an oxo radical in the 4-position.

The separation may be carried out according to any known method which is compatible with the molecule. By way of example, the separation may be carried out by preparation of an optically active salt, for example by the action of L-(+)- or D-(-)-mandelic acid, ditoluoyltartaric acid or dibenzoyltartaric acid, followed by separation of the isomers by

crystallization. The desired isomer is freed from its salt in a basic medium.

The compounds of general formula (I) may be purified, where appropriate, by physical methods such as crystallization or chromatography.

The compounds of formula (IV) the salts thereof, with the exception of compounds in which R^2 represents a phenyl group which is monosubstituted in the 2-position with alkyl or alkyloxy, are novel intermediates.

Compounds of formulae (I) and (IV) may be converted into addition salts with acids. Examples of addition salts with acids which may be mentioned are the salts formed with inorganic acids (hydrochlorides, hydrobromides, sulphates, nitrates and phosphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulphonates, p-toluensulphonates and isethionates, or with substitution derivatives of these compounds).

Substance P is known to be involved in a certain number of pathological fields. Agonists and antagonists of substance P, A.S. Dutta Drugs of the future, 12 (8), 782 (1987); Substance P and pain: an updating, J.L. Henry, TINS, 3 (4), 97 (1980); Substance P in inflammatory reactions and pain, S. Rosell, Actual. Chim. Ther., 12th series, 249 (1985); Effects of Neuropeptides on Production of Inflammatory Cytokines by Human Monocytes, M. Lotz et al., Science, 241, 1218 (1988); Neuropeptides and the pathogenesis of allergy, Allergy, 42, 1 to 11 (1987); Substance P in Human Essential Hypertension, J. Cardiovascular Pharmacology, 10 (suppl. 12), 5172 (1987).

Neurokinin A is known to be involved in a certain number of pathological fields such as asthma, the transmission of pain, headaches, migraine, inflammatory phenomena, arthritis, neurodegenerative mental disorders, neurological disorders, tension disorders, bladder disorders, cystitis, and painful and hypersecretory spasmodic manifestations of the digestive tract. [C.A. Maggi et al., Drugs of the Future; 18 (2), 155-158 (1993); C.A. Maggi et al., J.Auton. Pharmacol., 13, 23-93 (1993)].

The isoindole derivatives according to the present invention which simultaneously antagonize the effects of tachykinins on NK1 and NK2 receptors may more especially find application in the fields of analgesia, inflammation, asthma, allergies, on the central nervous system, on the cardiovascular system, on the immune system or as antispasmodic agents, as well as in the field of the stimulation of lachrymal secretions.

The compounds of the invention show an affinity for substance P receptors (NK1) at concentrations of between 0.5 and 1000 nM according to the technique adapted from D.G. Payan et al., J. of immunology, 133 (6), 3260-5 (1984): Stereospecific receptors for substance P on cultured human IM-9 lymphoblasts and using the computer program of McPherson et al., J. Pharmacol. Meth., 14, 213 (1985): Analysis of radioligand binding experiments.

The compounds according to the invention also show an affinity for the neurokinin A receptors (NK2) at concentrations of between 2 and 1000 nM (IC_{50}), demonstrated in the technique for evaluating the affinity for human NK2 receptor:
the affinity of products for human NK2 receptor was evaluated on a washed homogenate of insect cells

(Spodoptera frugiperda, SF_{21}) which expresses the NK2 receptor cloned from human jejunum. The expression of this receptor in the SF_{21} line is obtained by infection of cells using a recombinant baculovirus (BVE-hNK2) which possesses the gene of the NK2 receptor studied. The affinity of the products was measured by studying the possible inhibition of the specific binding of neurokinin A labelled with iodine-125 (^{125}I-iodohistidyl NKA) on these cell homogenates by different concentrations of product. The binding of iodinated NKA, in the absence or presence of the product to be evaluated, is measured by counting the radioactivity on a gamma counter after incubation for 60 minutes at 25°C in the presence of 0.1 nM of radioactive ligand and rapid filtration, under reduced pressure, of the incubation medium. The non-specific binding is defined in the presence of 5 µM of non-radioactive NKA. The concentration of product which inhibits the specific binding of the ligand by 50% (IC_{50}) is determined by non-linear regression using the computer program of G.A. McPherson, Analysis of radioligand binding experiments, A collection of computer programs for the IBM PC. J. Pharmacol., Neth., 14, 213-228 (1985).

In human therapy, the products according to the invention may be particularly useful in the treatment of pain of traumatic, post-surgical, menstrual or cephalic origin, in facial vascular pain (cluster headache) and in the treatment of migraines. The novel isoindole derivatives are also useful in the treatment of inflammation in rheumatology, in the treatment of rheumatoid arthritis and in complaints due to disruption of the immune system, in the treatment of inflammations in dermatology such as psoriasis, herpes, urticaria, eczema, photodermatosis, burns and in dental or ocular inflammatory complaints and in the field of lachrymal secretions; they are also useful in

the treatment of painful and inflammatory spasmodic manifestations of the digestive tract (ulcerative colitis, irritable bowel syndrome, Crohn's disease), the urinary system (urinary hyperreflexia, cystitis) and the respiratory system (asthma, bronchial hypersecretion, chronic bronchitis, rhinitis) and in tardive dyskinesias and antiemetic treatments. The products according to the invention may also find an application in the treatment of neurological diseases, Parkinson's disease, Alzheimer's disease, in the treatment of inflammatory and/or autoimmune and/or demyelinating diseases of the central and/or peripheral nervous system (multiple sclerosis, polyradiculitis, encephalopathies of viral origin etc.), in neurological syndromes related to a plasmatic extravasation (oedema of the spinal cord, cerebral oedema, etc.), in relation with an attack on the blood-brain barrier or in any spastic neurological syndrome (muscle-relaxing treatments). The products according to the invention may also be useful in the treatment of anxiety, psychosis, schizophrenia, Huntingdon's chorea, or alternatively in cardiovascular disorders such as hypotension. Another application may also be the treatment of gynaecological disorders, the treatment of disorders linked to poor growth regulation (dwarfism, hypotrophy secondary to chronic infant diseases, osteoporosis, the development of grafts).

Thus, in a further aspect, the present invention relates to a method for the treatment of conditions in which the action of tachykinins on NK1 and/or NK2 receptors is implicated comprising administering to a patient an effective amount of a compound of formula (I) or a salt thereof.

The present invention also relates to a pharmaceutical composition comprising a compound of general formula (I) or a salt thereof, optionally in combination with

any other pharmaceutically compatible product, which may be inert or physiologically active, such as a carrier or excipient.

Furthermore, the present invention relates to a pharmaceutical composition for the treatment of conditions in which the action of tachykinins on NK1 and/or NK2 receptors is implicated, more especially for the treatment of diseases or disorders of the respiratory system, comprising an effective amount of a compound of formula (I) or a salt thereof in association with a pharmaceutically acceptable carrier or excipient.

The present invention also relates to the use of a compound of formula (I) or a salt thereof for the manufacture of a medicament for the treatment of diseases or disorders of the respiratory system.

The compositions according to the invention may be used via the parenteral, oral, sublingual, rectal, topical, ocular or intranasal route or as aerosols for the lungs.

The sterile compositions for parenteral administration which may in particular be used in the form of infusions are preferably aqueous or non-aqueous solutions, suspensions or emulsions. Water, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents may be used as solvent or vehicle. These compositions may also contain adjuvants, in particular wetting, tonicity, emulsifying, dispersing and stabilizing agents. The sterilization may be achieved in several ways, for example by aseptic filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions

which may be dissolved at the time of use in an injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules, which contain, besides the active product, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

Tablets, pills, powders or granules may be used as solid compositions for oral administration. In these compositions, the active product according to the invention (optionally combined with another pharmaceutically compatible product) is mixed with one or more inert adjuvants or diluents, such as sucrose, lactose or starch. These compositions may also contain substances other than diluents, for example a lubricating agent such as magnesium stearate.

Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents such as water or paraffin oil may be used as liquid compositions for oral administration. These compositions may also contain substances other than diluents, for example wetting, sweetening or flavouring products.

The compositions for topical administration may, for example, be creams, ointments or lotions.

The compositions for ocular administration may be instillations or eyedrops.

The compositions for intranasal administration may be pharmaceutically acceptable powders or solutions which are intended for drops or for sprays.

The compositions may also be aerosols. For use in the form of liquid aerosols, the compositions may be

stable sterile solutions or solid compositions which are dissolved at the time of use into apyrogenic sterile water, serum or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols which are intended to be inhaled directly, the active principle is finely divided and is combined with a solid, water-soluble vehicle or diluent with a particle size of 30 to 80 μm, for example dextran, mannitol or lactose.

Inhalation devices from which non-pressurized formulations may be administered include the Spinhaler®. Powder formulations may also be inhaled from a pre-pierced capsule, e.g. as disclosed in WO 94/05560, using a device such as that disclosed in WO 94/19041. Alternatively, powder non-pressurized formulations may be inhaled from a device disclosed in EP 0 407 028 known as the "Ultrahaler" or directly from a disposable device such as that disclosed in EP 0 404 454 or from a device disclosed in WO 95/03846.

The formulation may alternatively be pressurized and contain a compressed gas, e.g. nitrogen, or a liquified gas propellant. Suitable propellants include the chlorofluorocarbons sold under the Trade Mark "Freon", which are non-toxic and have a boiling point below 20°C at atmospheric pressure. However, in view of environmental concerns, it may be preferable to use one of the hydrofluoroalkane propellants, for example, HFA-134a or HFA-227. Mixtures of the above-mentioned propellants may suitably be employed.

The pressurized formulation may also contain a surface active agent. When the propellant is a hydrofluoroalkane, the surface active agent may be a polymer soluble in the liquid hydrofluoroalkane, for example those polymers containing amide containing units and carboxylic acid ester containing units as

described in WO 93/05765.

The powder and pressurized formulations may also contain suitable flavouring, for example peppermint oil or menthol or combinations thereof, such as the commercially available product Dentomint™, or polysaccharide agents such as described in WO 93/17663. The powder and pressurized formulations may also comprise a sweetening agent, for example sugar, aspartame, cyclamates and saccharin and salts thereof, e.g. saccharin sodium.

The doses of drug substance to be administered will naturally depend upon the desired effect and the duration of the treatment. For an adult, they may generally be between 0.025 and 1500 mg per day in graded doses. Generally speaking however, the doctor will determine the dosage which he considers to be the most suitable, depending on the age, weight, and all the other personal factors of the subject to be treated.

The non-limiting examples which follow illustrate the present invention.

Intermediate 1

(3aR,7aR)-7,7-Diphenylperhydroisoindol-4-one mandelate

The title compound may be prepared according to the process described in European patent EP 429,366.

Intermediate 2

(3aR,7aR)-7,7-Diphenyl-2-tert-butoxycarbonyl-perhydroisoindol-4-one

To a suspension of 150 g of Intermediate 1 in 1000 cm^3 of dichloromethane, cooled to 0°C, was added with stirring 93.7 cm^3 of ethyldiisopropylamine followed by

a solution of 100 g of di-tert-butyldicarbonate in 250 cm^3 of dichloromethane. Stirring was continued for 10 minutes at this temperature and then for 90 minutes at a temperature of 20°C. 2.5 g of 4-dimethylamino-pyridine was added to the reaction medium and stirring was continued for 20 hours. The mixture was taken up in 500 cm^3 of water, 500 cm^3 of saturated aqueous sodium bicarbonate solution and 500 cm^3 of saturated aqueous sodium chloride solution. The organic phase was separated out after settling of the phases, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure (2.7 kPa) down to a residual volume of about 500 cm^3. This mixture was taken up in 500 cm^3 of ethyl acetate and 250 cm^3 of Merck silica gel (particle size 0.04-0.06 mm) and was then stirred for 20 minutes. The organic phase was filtered through a sinter funnel and the silica was washed with twice 250 cm^3 of ethyl acetate. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) and taken up with 500 cm^3 of a mixture of ethyl acetate and cyclohexane (50/50 by volume) and 200 cm^3 of Merck silica gel (0.04-0.06 mm). The mixture was stirred for 15 minutes, the organic phase was filtered through a sinter funnel and the silica was washed twice with 250 cm^3 of the same solvent mixture. The solution was concentrated to dryness under reduced pressure (2.7 kPa). The yellow oil obtained was crystallized from a mixture of 250 cm^3 of diisopropyl ether and 150 cm^3 of petroleum ether to yield 118.5 g of the title compound as white crystals, ($[\alpha]^{20}_D$ = -299.3°, c=1, MeOH, Na 589 nm).

Intermediate 3

(3aR,7aR)-7,7-Diphenyl-2-tert-butoxycarbonyl-4-triethylsilyloxy-2,3,3a,6,7,7a-(1H)-hexahydro-isoindole

To a stirred solution of 106 cm^3 of 2,2,6,6-tetramethylpiperidine in 1000 cm^3 of tetrahydrofuran, cooled to -5°C and under a nitrogen atmosphere, was added dropwise a solution of 394 cm^3 of 1.6M n-butyllithium in hexane. The mixture was cooled to a temperature of -75°C and a solution of 118 g of Intermediate 2 in 500 cm^3 of tetrahydrofuran was then run in. Stirring was continued for 45 minutes at this temperature and a solution of 106 cm^3 of triethylchlorosilane in 100 cm^3 of tetrahydrofuran was then run in. Stirring was continued for 2 hours at this temperature and the reaction medium was then allowed to rise to a temperature of 0°C and was then taken up with 500 cm^3 of saturated sodium bicarbonate solution. The organic phase was separated out after settling of the phases, washed with 500 cm^3 of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained was dissolved in 250 cm^3 of a mixture of cyclohexane and ethyl acetate (90/10 by volume). 200 cm^3 of Merck silica gel (particle size 0.04-0.06 mm) was added and the mixture was stirred for 15 minutes. The solution was filtered through a sinter funnel and the silica was washed twice with 900 cm^3 of the mixture of cyclohexane and ethyl acetate (90/10 by volume). The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) to yield 163.2 g of the title compound as a yellow oil.

Intermediate 4

(3aR,5R,7aR)-7,7-Diphenyl-2-tert-butoxycarbonyl-5-triethylsilyloxyperhydroisoindol-4-one

To a stirred solution of 163.2 g of Intermediate 3 in 2000 cm^3 of dichloromethane, cooled to a temperature of -10°C, was added portionwise 75.5 g of 80% 3-chloroperbenzoic acid. After stirring for one hour, a further 13 g of 80% 3-chloroperbenzoic acid was added at a temperature of 18°C. The stirring was continued for 90 minutes and the reaction medium was taken up in 500 cm^3 of saturated aqueous potassium bicarbonate solution and 500 cm^3 of saturated aqueous sodium chloride solution. The organic phase was separated off after settling of the phases, dried over anhydrous magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The yellow oil obtained was chromatographed on a column of Merck silica gel (particle size 0.04-0.06 mm, diameter 6 cm, height 36 cm), eluting at a pressure of 0.5 bar of nitrogen with a mixture of cyclohexane and ethyl acetate (90/10 by volume) and collecting 250 cm^3 fractions. Fractions 5 to 13 were combined and concentrated to dryness under reduced pressure (2.7 kPa) to yield 130 g of the title compound as an oil which crystallized.

Intermediate 5

(3aR,4R,5R,7aR)-7,7-Diphenyl-4-(2,5-dimethoxyphenyl)-2-tert-butoxycarbonyl-5-triethylsilyloxyperhydro-isoindol-4-ol

To a mixture of 49 g of 2,5-dimethoxyphenylmagnesium bromide in 200 cm^3 of tetrahydrofuran was added with stirring, at a temperature of 25°C, a solution of 61 g of Intermediate 4 in 150 cm^3 of tetrahydrofuran. The mixture was stirred for 15 hours at a temperature of

20°C and was then taken up in 500 cm^3 of saturated aqueous ammonium chloride solution. The precipitate formed was filtered off and the filtrate was taken up in 250 cm^3 of water and 250 cm^3 of saturated sodium chloride solution. The organic phase was separated out after settling of the phases, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained was dissolved in 1000 cm^3 of a mixture of cyclohexane and ethyl acetate (90/10 by volume). 500 cm^3 of Merck silica gel (particle size 0.04-0.06 mm) was added, the solution was filtered through a sinter funnel, the silica was washed with 3 times 1000 cm^3 of the solvent mixture and the filtrate was concentrated to dryness under reduced pressure (2.7 kPa) to yield 78 g of the title compound as a yellow oil.

Intermediate 6

(3aR,4R,5R,7aR)-4-(2,5-Dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol hydrochloride

To 500 cm^3 of 5.3N hydrochloric-dioxane solution was added with stirring, at a temperature of 20°C, a solution of 78 g of Intermediate 5 in 150 cm^3 of dioxane. The mixture was stirred for 5 hours at a temperature of 20°C and was then concentrated to dryness under reduced pressure (2.7 kPa). The residue was taken up in 100 cm^3 of absolute ethanol and cooled to 0°C. The precipitate was filtered off under vacuum and oven-dried at 40°C to yield 25.2 g of the title compound as white crystals.

Intermediate 7

4-(N-Methylbenzylamino)butyric acid hydrochloride

The title compound may be prepared by analogy with the

method described by R.K. RAZDAN et al in J. Med. Chem., Vol.19 (4), pp.454-61, 1976.

Intermediate 8

(3aR,4R,5R,7aR)-4-(5-Fluoro-2-methoxyphenyl) 7,7-diphenyl-2-tert-butoxycarbonyl-5-triethylsilyloxy-perhydroisoindole-4-ol

A solution of 20.84 g of Intermediate 4 in 50 cm^3 of tetrahydrofuran was added to a solution of 5-fluoro-2-methoxyphenylmagnesium bromide in 200 cm^3 of tetrahydrofuran (prepared from 41g of 2-bromo-4-fluoro anisole and 4.8 g of magnesium), and the reaction mixture was stirred at 20°C then poured in 200 cm^3 of a saturated aqueous solution of ammonium chloride. The precipitate formed was filtered and the filtrate diluted by addition of 250 cm^3 of water and 250 cm^3 of a saturated aqueous solution of sodium chloride. The organic phase was separated, dried on magnesium sulfate, filtered and evaporated under reduced pressure (2.7 kPa). The resulting oil was dissolved in 1000 cm^3 of a mixture of cyclohexane and ethyl acetate(90/10 v/v) and the solution treated with 500 cm^3 of silica gel (0.04-0.06 mm). The mixture was filtered and the silica washed 3 times with 1000 cm^3 of the same solvent mixture. The combined solutions were evaporated under reduced pressure (2.7 kPa) to give 31g of the title compound as a yellow oil.

Intermediate 9

(3aR,4R,5R,7aR)-4-(5-Fluoro-2-methoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol hydrochloride

To 100 cm^3 of a 8.1 N solution of hydrochloric acid in dioxane, a solution of 31 g of Intermediate 8 in 50 cm^3 of dioxane was added with stirring at a

temperature of 20°C. Stirring was maintained for 5 hours at the same temperature, and then the reaction mixture was concentrated under reduced pressure (2.7 kPa). The residue was diluted with 100 cm^3 of anhydrous ethanol and chilled at 0°C. The precipitate formed was filtered and dried in an oven at 40°C. to give 12.3 g of the title compound as a white solid.

Example 1

(3aR,4R,5R,7aR)-4-(2,5-Dimethoxyphenyl)-2-(4-dimethylaminobutyryl)-7,7-diphenylperhydroisoindole-4,5-diol

To a suspension of 2.6 g of Intermediate 6 in 100 cm^3 of dichloromethane were added with stirring, at a temperature of 5°C, 1 g of 4-dimethylaminobutyric acid hydrochloride, 1.24 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 20 mg of 1-hydroxybenzotriazole hydrate and 3 cm^3 of ethyldiisopropylamine. The mixture was stirred for 15 minutes at this temperature and then for 16 hours at 23°C. The solution obtained was washed with 200 cm^3 of water and twice with 200 cm^3 of saturated aqueous sodium chloride solution. The organic phase was separated out after settling of the phases, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The yellow foam obtained was chromatographed on a column of alumina (diameter 2.4 cm, height 16 cm), eluting at a pressure of 0.5 bar of nitrogen with a mixture of ethyl acetate and methanol (100/0 and then 95/5 by volume) and collecting 25 cm^3 fractions. Fractions 7 to 12 were combined and concentrated to dryness under reduced pressure (2.7 kPa). The yellow foam obtained was crystallized from 10 cm^3 of ethyl acetate. Filtration and two washes with 5 cm^3 of ethyl acetate yielded 0.54 g of the title compound as white crystals melting at 150°C.

Example 2

(3aR,4R,5R,7aR)-2-(4-Benzyldimethylammoniobutyryl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole 4,5-diol bromide

To a solution of 1 g of the product of Example 1 in 25 cm^3 of tetrahydrofuran was added with stirring, at a temperature of 20°C, 1.1 cm^3 of benzyl bromide. The mixture was stirred for 45 minutes and was then filtered under reduced pressure and the precipitate obtained was washed four times with 10 cm^3 of tetrahydrofuran. After oven-drying at 40°C, 1 g of the title compound was obtained as white crystals. ^1H NMR spectrum in DMSO+AcOD, T=393 K, δ in ppm (400 MHz): 2.05 (2H, m, CH_2), 2.10 and 2.25 (1H each, m and t, J=6Hz, $COCH_2$), 2.45 and 2.90 (1H each, t and t, J=12Hz, CH_2), between 2.7 and 3.7 (17H, m, 3 NCH_2, 2 CH, 2 NCH_3, 1 OCH_3), 3.73 (3H, s, OCH_3), 4.28 (1H, t, J=12Hz, OCH), 4.55 (2H, s, NCH_2Ph), 6.78 (2H, m, aromatic H), between 7.10 and 7.60 (16H, m, aromatic H).

Example 3

(3aR,4R,5R,7aR)-4-(2,5-Dimethoxyphenyl)-2-[4-(1-pyrrolidinyl)butyryl]-7,7-diphenylperhydro-isoindole-4,5-diol

Working as in Example 1, starting with 2 g of Intermediate 6 and 0.88 g of 4-(1-pyrrolidinyl)-butyric acid hydrochloride[1], 1.27 g of the title compound was obtained as a cream-coloured powder.

1. 4-(1-Pyrrolidinyl)butyric acid hydrochloride may be prepared according to the method described by R.K.

Razdan et al., J. Med. Chem., vol. 19(4), pp. 454-61, 1976.

Example 4

(3aR,4R,5R,7aR)-2-[4-(1-Methyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol iodide

Working as in Example 2, starting with 0.6 g of the product of Example 3 and 0.32 cm^3 of iodomethane, 0.5 g of the title compound was obtained as a pale yellow solid. ^1H NMR spectrum in DMSO+AcOD, T=393 K, δ in ppm (400 MHz): 1.98 (2H, m, CH_2), 2.12 (4H, m, $(CH_2)_2$), 2.13 and 2.25 (1H each, m, $COCH_2$), 2.43 and 2.90 (1H each, t, J=12Hz, CH_2), between 2.7 and 3.7 (18H, m, 5 NCH_2, 2 CH, 1 NCH_3, 1 OCH_3), 3.73 (3H, s, OCH_3), 4.28 (1H, t, J=12Hz, OCH), 6.78 (2H, m, aromatic H), between 7.10 and 7.60 (11H, m, aromatic H).

Example 5

(3aR,4R,5R,7aR)-2-[4-(1-Benzyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol bromide

Working as in Example 2, starting with 0.53 g of the product of Example 3 and 0.53 cm^3 of benzyl bromide, 0.5 g of the title compound was obtained in the form of a white solid. ^1H NMR spectrum in DMSO + AcOD, T=393 K, δ in ppm (400 MHz): 2.12 (4H, m, $(CH_2)_2$), 2.10 and 2.24 (1H each, m, CH_2), 2.43 and 2.90 (1H each, t, J=12Hz, $COCH_2$), between 2.7 and 3.7 (18H, m, 5 NCH_2, 2 CH, 1 OCH_3), 3.73 (3H, s, OCH_3), 4.28 (1H, t, J=12Hz, OCH), 4.53 (2H, s, NCH_2Ph), 6.78 (2H, m,

aromatic H), between 7.10 and 7.60 (16H, m, aromatic H).

Example 6

(3aR,4R,5R,7aR)-4-(2,5-Dimethoxyphenyl)-2-[4-(1-imidazolyl)butyryl]-7,7-diphenylperhydroisoindole-4,5-diol

Working as in Example 1, starting with 3.4 g of Intermediate 6 and 2.66 g of 4-(1-imidazolyl)butyric acid hydrochloride[2], 2.63 g of the title compound was obtained as a white foam.

2. 4-(1-Imidazolyl)butyric acid hydrochloride may be prepared according to the method described by J.P. Collman et al., J. Am. Chem. Soc., vol. 102(12), pp. 4182-92, 1980.

Example 7

(3aR,4R,5R,7aR)-2-[4-(3-Benzyl-1-imidazolio)butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindol-4,5-diol bromide

Working as in Example 2, starting with 0.7 g of the product of Example 6 and 0.7 cm^3 of benzyl bromide, 0.79 g of the title compound was obtained in the form of a white solid. ^1H NMR spectrum in DMSO + AcOD, T=403 K, δ in ppm (400 MHz): between 2.00 and 2.30 (4H, m, 2 CH_2), 2.45 and 2.85 (1H each, d and t respectively, CH_2), between 2.70 and 3.65 (11H, m, 3 NCH_2, 2 CH, 1 OCH_3), 3.73 (3H, s, OCH_3), 4.25 (3H, m, OCH and NCH_2), 4.51 (2H, s, NCH_2Ph), 6.78 (2H, m, aromatic H), between 7.10 and 7.70 (18H, m, aromatic H), 9.2 (1H, s, imidazole H).

Example 8

(3aR,4R,5R,7aR)-2-(3-Diethylaminopropionyl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol

Working as in Example 1, starting with 3.4 g of Intermediate 6 and 1.4 g of 3-diethylaminopropionic acid hydrochloride, 2.9 g of the title compound was obtained as a white foam.

Example 9

(3aR,4R,5R,7aR)-2-(3-Benzyldiethylammoniopropionyl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol bromide

Working as in Example 2, starting with 0.8 g of the product of Example 8 and 0.83 cm^3 of benzyl bromide, 0.66 g of the title compound was obtained as a white solid. ^1H NMR spectrum in DMSO + AcOD, T=403 K, δ in ppm (400 MHz): 1.32 (6H, t, J=6Hz, 2 CH_3), 2.48 and 2.90 (1H each, t, J=12Hz, CH_2), 2.70 and 2.85 (1H each, m, $COCH_2$), 2.43 and 2.90 (1H each, t, J=12Hz, $COCH_2$), between 3.10 and 3.70 (18H, m, 5 NCH_2, 2 CH, 1 OCH_3), 3.74 (3H, s, OCH_3), 4.25 (1H, t, J=12Hz, OCH), 4.51 (2H, s, NCH_2Ph), 6.78 (2H, m, aromatic H), between 7.10 and 7.60 (16H, m, aromatic H).

Example 10

(3aR,4R,5R,7aR)-4-(5-Fluoro-2-methoxyphenyl)-2-(4-dimethylaminobutyryl)-7,7-diphenylperhydroisoindole-4,5-diol

To a solution of 1 g of 4-dimethylaminobutyric acid hydrochloride and 1.05 cm^3 of ethyldiisopropylamine in 30 cm^3 of dichloromethane was added with stirring, at

a temperature of 3°C, 1 g of N,N'-carbonyldiimidazole. The mixture was stirred for 30 minutes at this temperature and then for 35 minutes at 23°C. A suspension of 2.6 g of Intermediate 9 and 0.96 cm^3 of ethyldiisopropylamine in 30 cm^3 of dichloromethane were then added. After stirring for 24 hours, the solution obtained was washed with 100 cm^3 of water and 100 cm^3 of saturated aqueous sodium chloride solution. The organic phase was separated out after settling, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The yellow oil obtained was chromatographed on a column of alumina (diameter 3 cm, height 13 cm), eluting at a pressure of 0.5 bar of nitrogen with a mixture of ethyl acetate and methanol (100/0 and then 95/5 by volume) and collecting 35 cm^3 fractions. Fractions 9 to 16 were combined and concentrated to dryness under reduced pressure (2.7 kPa) to give 1.3 g of the title compound as a white foam.

Example 11

(3aR,4R,5R,7aR)-2-(4-Benzyldimethylammonio-2-butyryl) 7,7-diphenyl-4-(5-fluoro-2-methoxyphenyl)perhydroiso-indole-4,5-diol bromide

To a solution of 0.5 g of the product of Example 10 in 10 cm^3 of tetrahydrofuran, 0.59 cm^3 of benzyl bromide was added at a temperature of 20°C with stirring. Stirring was continued for 45 minutes and then the obtained precipitate was filtered and washed twice with 5 cm^3 of tetrahydrofuran and once with 20 cm^3 of diisopropylether. After drying in an oven at 40°C, 0.52 g of the title compound was obtained as a white solid. ^1H NMR Spectrum in DMSO + AcOD solution, T=393K, δ in ppm (400 MHz): 2.05 (2H, m, CH_2), 2.08 and 2.25 (1H each, m, $COCH_2$), 2.47 and 2.90 (1H each,

t, J=12Hz, $COCH_2$), between 2.7 and 3.7 (14H, m, 3 NCH_2, 2 CH, 2 NCH_3, 1 OCH_3), 4.28 (1H, t, J=12Hz, OCH), 4.53 (2H, s, NCH_2Ph), 6.86 (1H, dd, J=4 and 7Hz, aromatic CH), 6.97 (1H, td, J=2 and 7Hz, aromatics CH), between 7.15 and 7.60 (16H, m, aromatic CH).

Example 12

(3aR,4R,5R,7aR)-4-(2,5-Dimethoxyphenyl)-2-[4-(N-methylbenzylamino)butyryl]-7,7-diphenyl perhydroisoindole-4,5-diol

A mixture of 0.974 g of Intermediate 7, 0.575 g of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, 10 mg of 1-hydroxybenzotriazole hydrate, 1.58 cm^3 of ethyldiisopropylamine and 0.963 g of Intermediate 6 in 50 cm^3 of dichloromethane, was stirred at a temperature of 23°C for 15 hours. The resulting mixture was separated by flash chromatography on alumina (column diameter 3 cm, height 14 cm), under nitrogen pressure (0.5 bar). Impurities were eluted with 500 cm^3 of a mixture of ethyl acetate and cyclohexane (60/40 v/v) and with 350 cm^3 of ethyl acetate. The expected compound was eluted with 300 cm^3 of a mixture of ethyl acetate and methanol (95/5 v/v). These fractions were evaporated under reduced pressure (2.7 kPa) to give a white foam which was dissolved in 15 cm^3 of ethyl acetate. The solid formed was filtered, the filtrate evaporated under reduced pressure (2.7 kPa) and the residue crystallized from 5 cm^3 of a mixture of ethyl acetate and cyclohexane to give 0.55 g of the title compound as a white solid. ^1H NMR spectrum in DMSO-d6 + CD_3CO_2D, T=403K, δ in ppm (400 MHz): 1.78 (2H, bm, CH_2), 2.03 and 2.18 (1H each, bm, CH_2CO), 2.30 (3H, s, NCH_3), 2.45 and 2.90 (1H each, respectively d, J=13Hz, and t,

J=13-13Hz, CH_2), 2.58 (2H, bm, NCH_2), 2.80 (1H, bm, CH), between 3.10 and 3.60 (8H, bm, OCH_3, CH and 2 NCH_2), 3.70 (2H, s, NCH_2Ph), 3.74 (3H, s, OCH_3), 4.28 (1H, dd, J=3 and 13Hz, CHO), 6.78 (2H, m, 2 CH aromatics), between 7.10 and 7.55 (16H, m, 16 CH aromatics).

Example 13

(3aR,4R,5R,7aR)-4-(5-Fluoro-2-methoxyphenyl)-2-[N-methylbenzylamino)butyryl]-7,7-diphenylperhydro-isoindole-4,5-diol

A mixture of 1.46 g of Intermediate 7, 0.766 g of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, 20 mg of 1-hydroxybenzotriazole hydrate, 2.26 cm^3 of ethyldiisopropylamine and 1.46 g of Intermediate 9 in 75 cm^3 of dichloromethane was stirred at a temperature of 23°C for 65 hours. The resulting mixture was separated by flash chromatography on alumina (column diameter 3 cm, height 14 cm) under nitrogen pressure (0.5 bar). Impurities were eluted with 500 cm^3 of a mixture of ethyl acetate and cyclohexane (60/60 v/v). The expected compound was eluted with 175 cm^3 of a mixture of ethyl acetate and methanol (95/5 v/v). These fractions were evaporated under reduced pressure (2.7 kPa) to give 1.1 g of the title compound as a white foam. ^1H NMR spectrum in DMSO-d6 + CD_3CO_2D, T=403K, δ in ppm (400 MHz): 1.75 (2H, bm, CH_2), 2.02 and 2.18 (1H each, bm, CH_2CO), 2.30 (3H, s, NCH_3), 2.45 and 2.90 (1H each, respectively d, J=13Hz, and t, J=13-13Hz, CH_2), 2.56 (2H, bm, NCH_2), 2.80 (1H, bm, CH), between 3.10 and 3.60 (8H, bm, OCH_3, CH and 2 NCH_2), 3.68 (2H, s, NCH_2Ph), 4.28 (1H, dd, J=3 and 13Hz, CHO), 6.85 (1H, dd, J=4-8Hz, CH arom.), 6.95 (1H, dt, J=3-8-8Hz, CH

aromatic), between 7.10 and 7.55 (16H, m, 16 CH aromatics).

IN VIVO RESULTS

1) Injection of neurokinin A into guinea pigs gives rise to a bronchospasm. The bronchoconstriction induced in vivo in guinea pigs by injection of capsaicin, neurokinin A or of a selective neurokinin A agonist: [$Lys^5MeLeu^9Nle^{10}$]NKA(4-10), was studied, for example, according to the technique of H. Konzett and R. Rosseler, Archiv. Exp. Path. Pharmak., 195, 71-74 (1940). This bronchoconstriction was inhibited by injection of a product according to the invention, which is evidence of antiasthmatic activity. The percentage inhibition of the bronchospasm induced by 0.075 µg/kg i.v. of [$Lys^5MeLeu^9Nle^{10}$]NKA(4-10) was determined. In this study, the percentage inhibition of the product of Example 1 was 60% at a dose of 0.1 mg/kg i.v.

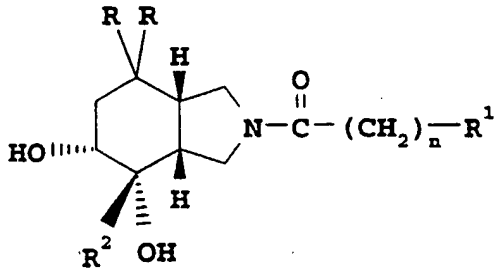
2) Pulmonary inflation pressure (PIP) was determined in anaesthetised guinea pigs pretreated with atropine (1mg/kg i.v.). Capsaicin (20 nmol/kg i.v.) was administered three times at 30 minute intervals and the change in PIP recorded. Compounds of the invention or vehicle (10% PEG 400 in saline) were administered 30 minutes prior to the second capsaicin dose. The response to capsaicin was calculated as the change in PIP from the basal level and the effect of the neurokinin antagonist or vehicle as % change from the initial control capsaicin response. In this study, the compounds of Examples 1, 9 and 11 had ID_{50} values of 340µg/kg, 28µg/kg and 170µg/kg respectively.

Guinea pigs treated with compounds of the invention showed no overt toxic effects at the highest tested

doses i.v. of 1mg/kg and up to 30mg/kg p.o.

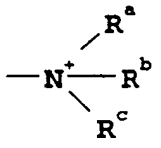
CLAIMS

1. A compound of the general formula (I):



(I)

and salts and solvates thereof wherein
- the moieties R are identical and represent phenyl radicals optionally substituted in the ring 2 or 3 position with a fluorine or chlorine atom or a methyl group;
- R^1 represents a group $-NR^aR^b$ or an ammonio radical of structure:



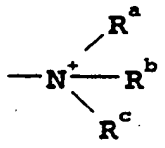
, X^- (II)

in which X^- is an anion and R^a, R^b and R^c are the same or different and each independently represents a C_{1-4}alkyl or arylC_{1-4}alkyl group, or R^a and R^b, together with the nitrogen atom to which they are attached, form a saturated 4- to 6-membered heterocycle optionally containing a heteroatom selected from O, S, NH or NR^d (where R^d is C_{1-4}alkyl or arylC_{1-4}alkyl) in place of one of the ring CH_2 groups; or when R^1 represents a group $-NR^aR^b$ then R^a and R^b, together with the nitrogen atom to which they are attached, may also form an unsaturated 4- to 6-membered heterocycle optionally containing a

heteroatom selected from O, S or N in place of one of the ring carbon atoms, or R^a and R^b, together with the nitrogen atom to which they are attached, may form a salt of an unsaturated 4- to 6-membered heterocycle wherein one of the ring carbon atoms is replaced with a group NR^d where R^d is as defined previously;
- R^2 represents a phenyl radical optionally substituted by one or more of halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy moieties; and
- n represents an integer from 2 to 4.

2. A compound according to Claim 1 in which R represents phenyl.

3. A compound according to Claim 1 or Claim 2 in which R^1 represents an ammonio radical of structure:



, X^- (II)

wherein R^a, R^b, R^c and X^- are as defined in Claim 1.

4. A compound according to Claim 3 in which R^c represents phenylC_{1-4}alkyl and R^a and R^b each independently represents C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated 4- to 6-membered heterocycle.

5. A compound according to Claim 4 in which R^c represents benzyl and R^a and R^b each independently represents C_{1-4}alkyl.

6. A compound according to any previous claim in which R^2 represents a mono- or disubstituted phenyl

moiety, where the substituent(s) is/are selected from halogen atoms and C_{1-4}alkyloxy groups.

7. A compound according to Claim 6 in which R^2 represents a phenyl moiety substituted in the ring 2-position and in the ring 5-position.

8. A compound according to Claim 7 in which R^2 represents 2,5-dimethoxyphenyl or 5-fluoro-2-methoxyphenyl.

9. A compound according to any previous claim in which n is 2 or 3.

10. (3aR,4R,5R,7aR)-2-(4-Benzyldimethylammonio-butyryl)-4-(2,5-dimethoxyphenyl)-7,7-diphenyl-perhydroisoindole-4,5-diol bromide;
(3aR,4R,5R,7aR)-2-[4-(1-methyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol iodide;
(3aR,4R,5R,7aR)-2-[4-(1-benzyl-1-pyrrolidinio)-butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydro-isoindole-4,5-diol bromide;
(3aR,4R,5R,7aR)-2-[4-(3-benzyl-1-imidazolio)butyryl]-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindol-4,5-diol bromide; and
(3aR,4R,5R,7aR)-2-(3-benzyldiethylammoniopropionyl)-4-(2,5-dimethoxyphenyl)-7,7-diphenylperhydroisoindole-4,5-diol bromide; and solvates thereof.

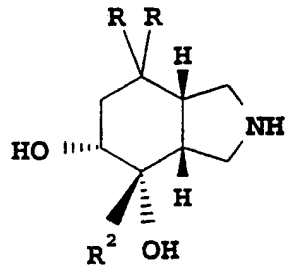
11. A salt of (3aR,4R,5R,7aR)-2-(4-benzyldimethyl-ammoniobutyryl)-7,7-diphenyl-4-(5-fluoro-2-methoxy-phenyl)-perhydroisoindole-4,5-diol.

12. (3aR,4R,5R,7aR)-2-(4-Benzyldimethylammonio-butyryl)-7,7-diphenyl-4-(5-fluoro-2-methoxyphenyl)-perhydroisoindole-4,5-diol bromide.

13. A process for the preparation of a compound according to Claim 1 comprising reacting a compound of formula (III):

$$R^1\text{-}(CH_2)_n\text{-}COOH \qquad (III)$$

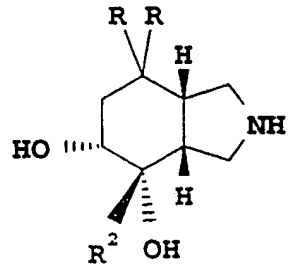
or a reactive derivative thereof (in which n is as defined in Claim 1 and R^1 is a group NR^aR^b) with a compound of formula (IV):



(IV)

(in which R and R^2 are as defined in Claim 1) or a salt thereof, followed, where required, by quaternization of the product thus obtained.

14. A compound of formula (IV):



(IV)

and salts thereof, in which R is as defined in Claim 1 and R^2 is as defined in Claim 1 except that R^2 cannot represent phenyl monosubstituted in the ring 2-position by C_{1-4}alkyl or C_{1-4}alkyloxy.

15. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1 or

a salt thereof in association with a pharmaceutically acceptable carrier or excipient.

16. A pharmaceutical composition for the treatment of diseases or disorders of the respiratory system comprising an effective amount of a compound according to Claim 1 or a salt thereof in association with a pharmaceutically acceptable carrier or excipient.

17. Use of a compound according to Claim 1 or a salt thereof for the manufacture of a medicament for the treatment of diseases or disorders of the respiratory system.

18. A method for the treatment of conditions in which the action of tachykinins on NK1 and/or NK2 receptors is implicated comprising administering to a patient an effective amount of a compound according to Claim 1 or a salt thereof.

19. A compound substantially as hereinbefore described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

nal Application No
CT/IB 96/00783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/44 A61K31/40 C07D233/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 22822 (RHONE-POULENC RORER S.A.) 13 October 1994 cited in the application see claims ---	1,15
A	WO,A,93 21155 (RHONE-POULENC RORER S.A.) 28 October 1993 cited in the application see claims -----	1,15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 1996	08. 10. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9422822	13-10-94	FR-A-	2703679	14-10-94
		AU-A-	6506894	24-10-94
		CZ-A-	9502584	17-01-96
		EP-A-	0693059	24-01-96
		FI-A-	954730	17-11-95
		NO-A-	953913	02-10-95
		PL-A-	310948	08-01-96
WO-A-9321155	28-10-93	FR-A-	2689888	15-10-93
		AU-B-	667214	14-03-96
		AU-A-	3956593	18-11-93
		CZ-A-	9402482	15-11-95
		EP-A-	0635003	25-01-95
		FI-A-	944729	07-10-94
		HU-A-	71354	28-11-95
		JP-T-	7505410	15-06-95
		NO-A-	943692	03-10-94
		NZ-A-	251730	28-08-95
		SK-A-	122094	10-05-95
		US-A-	5484804	16-01-96
		ZA-A-	9302527	08-11-93